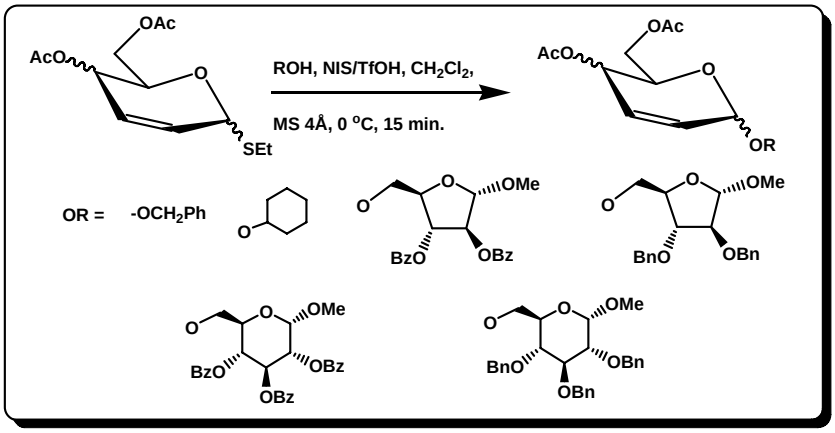
SYNOPSIS

Unsaturated sugars constitute as an important category of carbohydrate precursors in synthesis. Specifically, 1,2- and 2,3-unsaturated glycosides are excellent intermediates to derivatize monosaccharides and as building blocks in organic synthesis. For example, a major utility of 1,2-unsaturated sugars, namely glycals, is the addition reactions to afford 2-deoxy glycosides under acidic conditions and rearrangement reactions to produce 2,3-unsaturated glycosides. Lewis acids favour the formation of 2,3-unsaturated glycosides, whereas, Brønsted acids lead to normal addition products. A mixture of both the product is obtained often, depending on the nucleophiles and the stereochemistry of glycal. **Chapter 1** of the thesis describes (i) reactivities of glycals under acidic condition and (ii) a general survey of reactions involving on *C*2-*C*3 carbons of monosaccharides.

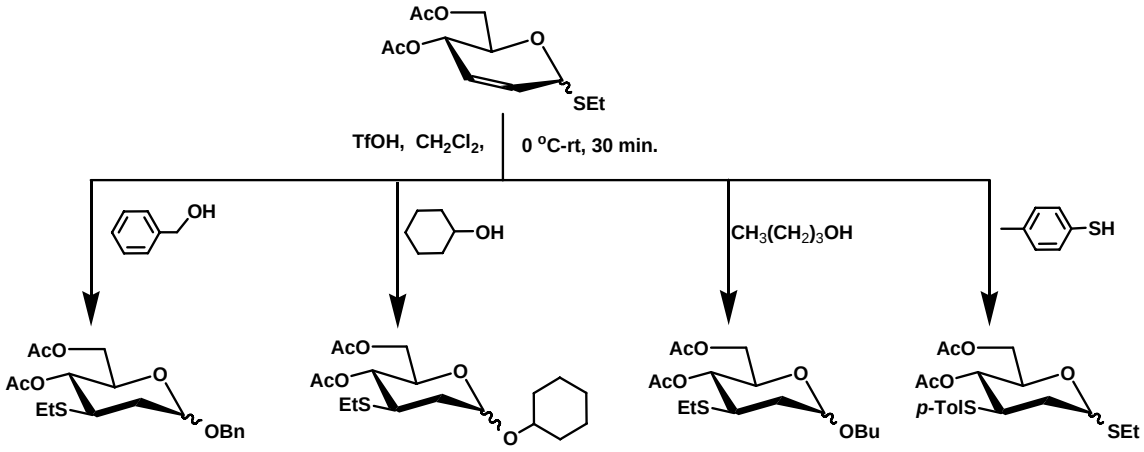
Glycals are useful precursors to derive a number of functionalized monosaccharide derivatives. A well-known acid catalyzed reaction of glycals is their conversion to 2,3-unsaturated glycosides, known as the Ferrier products. In a research programme, reactivity switching and selective activation of *C*-1 or *C*-3 of 2,3-unsaturated thioglycosides under acid catalyzed condition was undertaken. Thioglycosides are excellent glycosyl donors and can be activated easily. In identifying the reactivities of 2,3-unsaturated thioglycosides, obtained through Ce(IV)-mediated reaction of a glycal, it was intended to study the glycosylation reaction and also the reactivity control of *C*1-*C*3 carbons during a glycosylation reaction. Experiments showed that a reactivity switching was possible through activation of either *C*-1 or *C*-3. Thus, *C*-1 glycosylation with alcohol acceptors occurred in the presence of NIS/TfOH, without the acceptors reacting at *C*-3. On the other hand, reaction of 2,3-unsaturated thioglycosides with alcohols mediated by triflic acid alone led to a transposition of *C*-1 ethylthio-moiety to *C*-3 intramolecularly, to form 3-ethylthio-glycals. Resulting glycals underwent glycosylation with alcohols to afford 3-ethylthio-2-deoxy glycosides. However, when thiol was used as an acceptor, only a stereoselective addition at *C*-3 resulted, so as to form *C*-1, *C*-3 dithio-substituted 2-deoxypyranosides. Oxocarbenium ion is the reactive intermediate during activation of a glycosyl donor, and in the case of a 2,3-unsaturated thioglycosides, the oxocarbenium ion may stabilize further by the presence of a *C*2-*C*3 unsaturation. Reaction of a nucleophile with allylic oxocarbenium ion may lead to two regio-isomers. Initially, NIS/TfOH was attempted on 2,3–unsaturated sugar with various alcohols and it was found that *C*-1 was the preferred reactive centre (**Scheme 1**)

Scheme 1



In order to optimize the reaction for selective nucleophilic attack at *C*-3, further study was continued by using stoichiometric TfOH, in presence of acceptors alcohols with the intension to activate the double bond. The reaction led to the formation of 2-deoxy *O*-glycosides with the concomitant transposition of *C*-1 ethylthio-moiety to *C*-3 (**Scheme 2**).

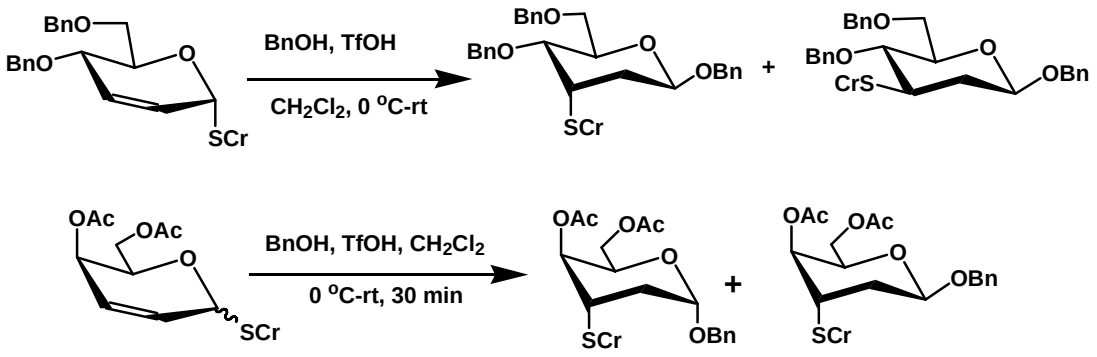
Scheme 2



An important observation was that the transposition of thioethyl group from *C*-1 to *C*-3 was highly regioselective. For example, with thiocresol as the nucleophile, there was an addition across the *C*-2-*C*-3 double bond to afford *C*-1, *C*-3-dithio derivative (**Scheme 2**). Thus, hard-soft nature of the nucleophiles, as well as, carbon centres helped to rationalize the reactivites.

It was also observed that the intramolecular transposition of thioethyl group is highly stereo-controlled by equatorial *C*-4 acetoxy group. Thus, thioethyl nucleophile approached selectively at *C*-3 and afforded *trans*-diequatorial products. This rationalization was further confirmed through (i) reaction of benzyl protected 2,3-unsaturated thioglycoside**,** wherein a *C*-3 epimeric mixture was observed in 1:1 ratio; (ii) galactosyl derivative under similar reaction condition afforded anomeric mixture of 3-(4-methylphenylthio)-*O*-glycosides**,** with *trans*-diaxial orientation of substituent at *C*-3 (**Scheme 3**).

Scheme 3

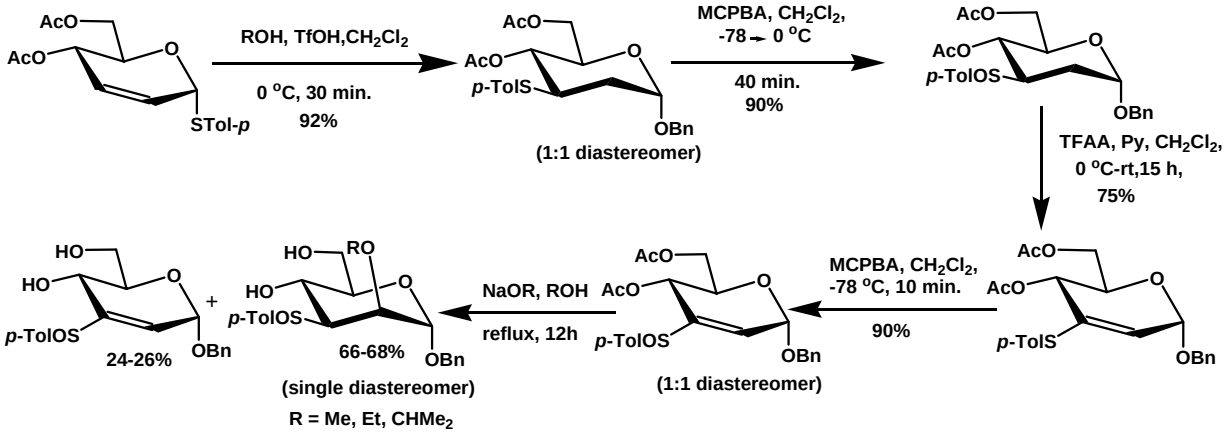


These reactions confirmed the role of *C*-4 substituent on the carbocation at *C*-3, through the presence or absence of a neighbouring group participation. In summary, in **Chapter 2** the selective activation of either anomeric carbon or *C*-3 with proper choice of activation and reactivity control at each carbon will be described.

Thioglycosides are excellent glyosyl donor and their glycosylation reactions were well explored. Upon indentifying the intramolecular transposition of thioalkyl/aryl functionality from *C*-1 to *C*-3, further investigations was undertaken to utilize the newly formed carbon sulfur bonds at *C*-3. Realizing a potential for such 3-alkyl/aryl thio 2-deoxy sugar, the Pummerer rearrangement was investigated. For this purpose, the thioalkyl/aryl moiety at *C*-3 was oxidized first to a sulfoxide. The resulting sulfoxide was allowed to undergo Pummerer rearrangement to afford vinyl sulfide (**Scheme 4**), resulting from the elimination of HOAc in the thioacetal formed *in situ*. Having implemented Pummerer rearrangement on a sugar substrate, synthetic utility of the rearrangement product, namely vinyl sulfide was undertaken.

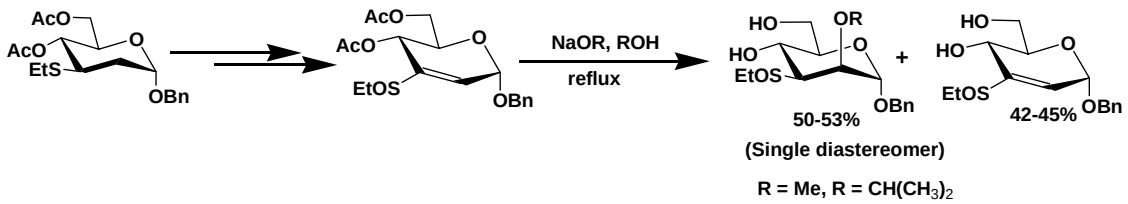
An effort to implement conjugate addition reaction was undertaken, which required the conversion of vinyl sulfide to vinyl sulfoxide in the first step. The conjugate addition reactions were first conducted with alkoxide nucleophiles. The reaction showed that addition of nucleophiles occurred from axial face to furnish *manno*-configured derivatives as a single diastereomer at sulfinyl sulfur in a moderate yield along with *O*-deacetylated product. It was also found that *O*-benzyl protected sugar vinyl sulfoxide was totally resistant to the conjugate addition reaction (**Scheme 4)**.

Scheme 4



In order to find the influence of the substituents in sulfoxide moiety in the addition of nucleophiles, additional study was conducted in which a less hindered thioethyl moiety was installed in place of *p*-tolylthio moiety. To install ethylthio moiety, a similar sequence of reaction was undertaken as described previously in **Scheme 4**. Conjugate addition reaction with alkoxide nucleophiles was conducted and analysis of the reaction showed that the addition of alkoxides remained similar, leading to the formation of *manno*-configuration of substituents (**Scheme 5**).

Scheme 5

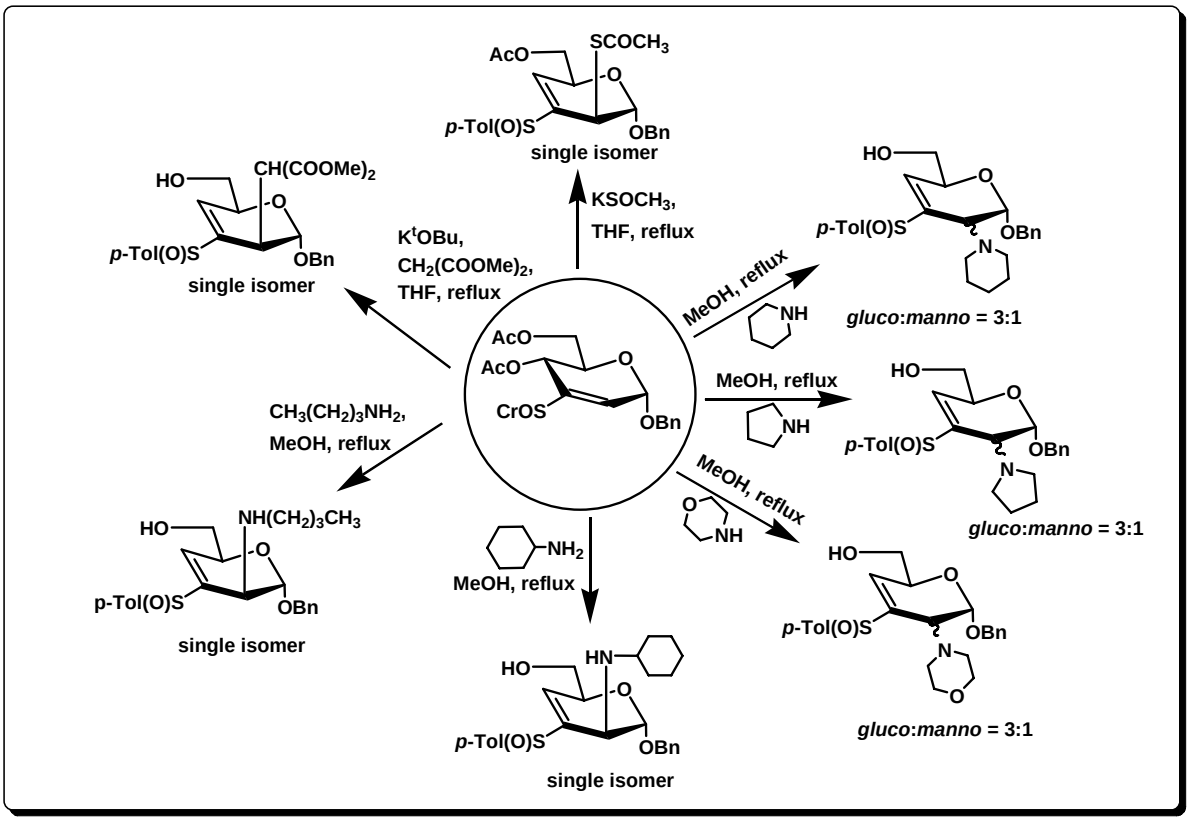


The configuration of the Michael adducts were ascertained from ^{1}H NMR, as well as 2D NMR spectroscopies. H-1 of all adducts appeared as an apparent singlet, consistent with very small $J_{1,2}$ values. Aryl vinyl sulfoxide afforded conjugate addition product at much higher ratio than corresponding alkyl vinyl sulfoxide. Thus, among aryl and alkyl vinyl sulfoxides, conjugate addition occurred better with the aryl vinyl sulfoxide, indicating a strong electronic effect of aryl group in stabilizing the conjugate anion which would form *in situ* during nucleophilic addition with vinyl sulfoxide. Therefore, *p*-tolylthio substituted vinyl sulfoxide served as a more efficient Michael acceptor when compared to the thioethyl substituted vinyl sulfoxide.

Asymmetric environment of vinyl sulfoxides play a vital role during the reaction. Vinyl sulfoxides can exist in two stereochemically distinct conformation which makes the vinyl group electronically dissimilar. In one of the conformer S-O and C-C bonds are coplanar, whereas in the other conformation, these two bonds are opposite to each other. It is agreed generally that vinyl sulfoxides generally try to adopt the most reactive conformer during the reaction in which the C-C and S-O bonds are *syn* to each other. Thus, the preference for an axial attack would originate from a face *anti* to the lone pair of electrons on the sulfur of sulfoxide functionality, leading to the formation of the product with *manno*-configuration. As *O*-deacetylated vinyl sulfoxide was obtained along with the Michael adducts, it was assumed that one of the epimers of vinyl sulfoxide appeared to be more reactive when compared to the other. **Chapter 3** describes implementation of a Pummerer rearrangement in order to synthesize a sugar vinyl sulfoxide and its conjugate addition reactions with alkoxide nucleophiles.

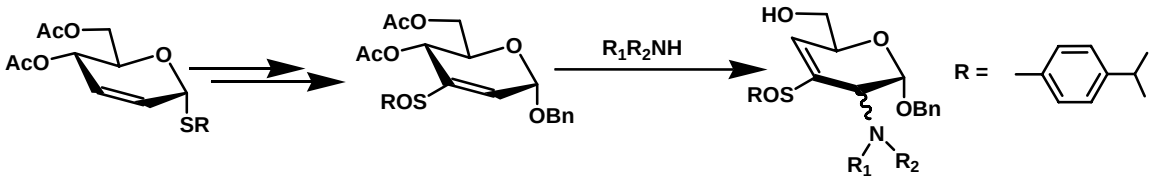
The nucleophilic addition reactions of vinyl sulfoxide with other nucleophiles were studied further. The effect of the substituents of chiral sulfoxides in conjugate addition reactions was also incorporated in the course of reactions. Reactions of amines, carbon and sulfur nucleophiles were undertaken with *p*-tolylthio-substituted vinyl sulfoxides. The reactions showed formation of the addition-elimination products (**Scheme 6**). All primary amines, carbon and sulfur nucleophiles afforded *C*-2 axial epimer, namely, *threo*-epimer exclusively, wherein secondary amines furnished the equatorial *vs* axial epimer in 3:1 ratio.

Scheme 6



In order to assess the course of the reaction, vinyl sulfoxide presenting a *p*-cumenethio- moiety was installed in place of *p*-tolylthio moiety. Conjugate addition reactions were performed with both primary as well as secondary amines that showed formation of the *C*-2 epimeric mixtures. With both the primary and secondary amines *C*-2 equatorial epimer was found to be as the major product (**Scheme 7**).

Scheme 7



In conjugate addition of vinyl sulfoxides, nucleophiles approach the olefinic face preferentially, which is *anti* to the electron rich sulfur lone pair of electrons and *syn* to the bulky aryl group. Therefore, *C*-2 *axial* epimer was observed as most favourable product. However, secondary amines remarkably influenced the pattern as well as selectivity of the reaction. Steric considerations were likely to dictate the overall reactivity with secondary amines which was even more pronounced when using *p*-cumenethio-substituted vinyl sulfoxide. **Chapter 4** describes the conjugate additions as well as remote effect of aryl substituent on the selectivity of addition of amines on sugar sulfoxide

In summary, the Thesis establishes:

- A new reactivity of switching and a selective activation of 2,3-unsaturated thioglycoside;
- A Pummerer rearrangement route in order to synthesize sugar vinyl sulfide for the first time, which on selective oxidation furnish a sugar vinyl sulfoxide, a useful precursor for conjugate addition reactions;
- An assessment of the stereoelectronic, as well as, steric effect of the chiral vinyl sulfoxide with various nucleophiles in conjugate addition reactions;
- Influence of the protecting groups were also studied in conjugate addition reactions.

Overall the study presented in the Thesis provides a new insight to unsaturated sugars. The salient features of the present findings also showed that the intermediates such as *C*-3 substituted thioalkyl/aryl glycosides, vinyl sulfides, a variety of new *C*-2 substituted vinyl sulfoxides are also the potential sites for many types of modifications in monosaccharides.

The following publications and presentations were based on the Thesis work:

1. **Mukherjee, A**.; Jayaraman, N. "Reactivity switching and selective activation of *C*-1 or *C*-3 in 2,3-unsaturated thioglycoside", *Carbohydr. Res*. **2011**, *12*, 1669-1575.

2. **Mukherjee, A**.; Jayaraman, N. "2,3-Unsaturated enoses. A Pummerer rearrangement route to sugar vinyl sulfides and synthesis of 3-deoxy-3-alkyl/arylsulfinyl pyranosides", *Tetrahedron* **2012**, *68*, 8746-8752.

3. **Mukherjee, A**.; Jayaraman, N. “Conjugate addition of sugar vinyl sulfoxide with nitrogen, carbon and sulfur derived nucleophiles”, Manuscript submitted.

4. **Mukherjee, A**.; Jayaraman, N. Reactivity switching and selective activation of *C*-1 or *C*-3 in 2,3-unsaturated thioglycoside”, Oral presentation on Pfizer Symposium on Organic Chemistry and Prof. D. K. Banerjee Memorial Award Lectures, Jan 2012, IISC-Bangalore, India.

5. Jayaraman, N.; **Mukherjee, A**. “Studies of 1,2-Unsaturated Sugars Through Expansion, Shifts and Rearrangements”, Oral presentation in 26th International Carbohydrate Symposium, July 2012, Madrid, Spain.